

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Cost-effectiveness of emergency preparedness measures in response to infectious respiratory disease outbreaks: a systematic review and econometric analysis
<b>AUTHORS</b>	Vardavas, Constantine; Nikitara, Katerina; Zisis, Konstantinos; Athanasakis, Konstantinos; Phalkey, Revati; Leonardi-Bee, Jo; Johnson, Helen; Tsovala, Svetla; Ciotti, Massimo; Suk, Jonathan

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Shorr, Andrew MedStar Washington Hospital Center, Medicine
<b>REVIEW RETURNED</b>	10-Nov-2020

<b>GENERAL COMMENTS</b>	<p>This paper is an economic review of various prevention and preparedness efforts relative to a respiratory infection outbreak. Not surprisingly, most prevention interventions are cost effective by nearly any measure. In this sense the paper seems a summary of many self-fulfilling prophecies. I have several concerns.</p> <ol style="list-style-type: none"><li>1. The paper needs to be edited for English language</li><li>2. The authors present the studies they are describing but make little effort to illustrate the strengths and weakness of these studies. This is what the "health officer" as a reader that they target really needs. For example, how well done is the simulation - what did it leave out or assume? Similarly, how generalizable are findings from Aus/NZ to the OECD? Rather than just a cursory summary of the study included, the authors need to put in the actual text how the study brings value.</li><li>3. In that same vein, they fail to put confidence intervals around any of the point estimates that drive the reviewed studies or the final conclusions of those studies. Readers require a fair assessment of the uncertainty in the authors conclusions so as to put things in context.</li><li>4. There are many added limitations to their approach that are not mentioned in their limitations section -- this needs to be expanded up significantly.</li></ol>
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<b>REVIEWER</b>	Ikai, Hiroshi Kyoto Prefectural University of Medicine, JAPAN
<b>REVIEW RETURNED</b>	26-Nov-2020

<b>GENERAL COMMENTS</b>	The research topic is politically important, the method is sound and extensive, and the interpretation of the results is reasonable. It is of great interest for those who describe the various measures to prevent the public from COVID-19.
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	Two minor points: (Page 13, line 10-12) as also -> 'as well as' is better understood. (page 30, query 41) I assume you combined '28-40', not '28-39).
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<b>REVIEWER</b>	Palumbo , Aimee Drexel University, Epidemiology & Biostatistics
<b>REVIEW RETURNED</b>	30-Nov-2020

<b>GENERAL COMMENTS</b>	<p>Thank you for the opportunity to review this article. I think the authors perform a critical analysis of the cost of interventions that can generally inform preparedness and public health strategies. Some aspects of the study that could improve the write up even further are described below.</p> <ol style="list-style-type: none"> <li>1. Justification for excluding South Korea and Japan should be explicitly stated.</li> <li>2. In the appendix of searches, it's not clear why the authors' included terms for non-respiratory illnesses such as HIV/AIDS, rabies, salmonella, listeriosis, and more in the searches and ultimately these searches yielded too many results to be practical. Were 20K+ title and abstracts screened? A brief summary of the considering only 66 out of 20K+ records screened were assessed. Without re-doing the search, a clearer summary of the main criteria used to move an article from screening to full text review would be helpful.</li> <li>3. Page 4, line 59 – the agreement % (837%) needs to be corrected</li> <li>4. In the description of the process used to analyze the synthesis of cost-effectiveness, an statement of the usual comparator would be helpful (e.g. “no intervention”) would be helpful because the description of more, equally, or less effective or costly begs the question of “compared to what?” It's mentioned later, but would be helpful to describe earlier.</li> <li>5. When describing the quality of the studies included (top of page 6), what were the reasons the one study was only of medium quality?</li> <li>6. For Appendices 2-4, labels are needed on the X axis</li> <li>7. Figure 2 – explanation of the color coding is needed in the footnote</li> <li>8. On page 8, Madema is referred to with the incorrect reference number (33). And is this a simulation model among developing countries? (in the table description it says 'developed')</li> <li>9. I think in general the reference numbers need to be double checked an updated.</li> <li>10. In the discussion of the stockpile strategy, was the cumulative costs over time taken into account? It seems like an important factor since the cost of maintaining it accumulates over years in which it is not needed, or at least talk about the average amount of time that the stockpiles remain unused.</li> <li>11. I think some important limitations need to be mentioned given that this will inevitably be discussed in light of COVID-19. Specifically, the typical duration of the outbreak or the simulation, and/or the availability of pharmaceutical interventions such as vaccination, would have a substantial impact on both compliance with non-pharmaceutical interventions and on the economic impact of closures, with the acknowledgement that the long-term effects of potential school drop-out or business closures could not be assessed.</li> </ol>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

### Comments to the Author

This paper is an economic review of various prevention and preparedness efforts relative to a respiratory infection outbreak. Not surprisingly, most prevention interventions are cost effective by nearly any measure. In this sense the paper seems a summary of many self-fulfilling prophecies. I have several concerns.

Comment 1: The paper needs to be edited for English language.

Response: Thank you for pointing this issue out. We carefully edited the text accordingly.

Comment 2: The authors present the studies they are describing but make little effort to illustrate the strengths and weakness of these studies. This is what the "health officer" as a reader that they target really needs. For example, how well done is the simulation -- what did it leave out or assume? Similarly, how generalizable are findings from Aus/NZ to the OECD? Rather than just a cursory summary of the study included, the authors need to put in the actual text how the study brings value.

Response: The purpose of this review was not to assess the strength and weakness of each identified study but to compare, using a comparable currency (Euro2017) the cost effectiveness of pharmaceutical and non pharmaceutical interventions in comparison to an unmitigated pandemic as outlined in the DRM approach. Each study provides valuable information on the intervention, and with the exclusion of the two East Asian countries (Japan/S Korea), the results are generalizable. Nevertheless we have noted this now in the methods and the limitations section respectively.

Comment 3: In that same vein, they fail to put confidence intervals around any of the point estimates that drive the reviewed studies or the final conclusions of those studies. Readers require a fair assessment of the uncertainty in the authors conclusions so as to put things in context.

Response: Once again thank you for your suggestions. We did not perform a pooled analysis of the data from which to derive confidence intervals, due to study heterogeneity (different interventions, different settings etc) and due to study design (systematic review). Hence it is not possible to create confidence intervals – as we report what the actual studies reported in each case but using a comparable cost measurement, the Euro in 2017. The original studies have not provided confidence intervals, but ranges which are included in Table 1. As for the levels of uncertainty, in most studies is assessed through sensitivity analyses presented in Appendix 5. Due to already extensive data and the word limitations imposed, we chose not to refer in depth to the uncertainty analyses in the main text.

Comment 4: There are many added limitations to their approach that are not mentioned in their limitations section -- this needs to be expanded up significantly.

Response: Thank you for your important comment. We included additional limitations in this section, such as publication bias due to the exclusion of non-English published studies, studies published before the pre-planned timeframe, the exclusion of seasonal influenza outbreaks and the exclusion of COVID-19.

Reviewer: 2

Comments to the Author

The research topic is politically important, the method is sound and extensive, and the interpretation of the results is reasonable. It is of great interest for those who describe the various measures to prevent the public from COVID-19.

Two minor points:

Comment 1: (Page 13, line 10-12) as also -> 'as well as' is better understood.

Response: Modified

Comment 2: (page 30, query 41) I assume you combined '28-40', not '28-39).

Response: Modified

Reviewer: 3

Comments to the Author

Thank you for the opportunity to review this article. I think the authors perform a critical analysis of the cost of interventions that can generally inform preparedness and public health strategies. Some aspects of the study that could improve the write up even further are described below.

Comment 1: Justification for excluding South Korea and Japan should be explicitly stated.

Response: Thank you for highlighting that. Korea and Japan were excluded, although belonging to OECD countries, due to the cultural differences with western countries and more specifically with Europe which was the main geographical area of interest. This clarification has been added in the 'Methods' section. The main reason for this exclusion was the fact that this work was produced under contract by the European Center for Disease Prevention and Control under specific contract No. 1 ECD.9630 within Framework contract ECDC/2019/001. This is now written in the methods, limitation and acknowledgements

Comment 2: In the appendix of searches, it's not clear why the authors' included terms for non-respiratory illnesses such as HIV/AIDS, rabies, salmonella, listeriosis, and more in the searches and ultimately these searches yielded too many results to be practical. Were 20K+ title and abstracts screened? A brief summary of the considering only 66 out of 20K+ records screened were assessed. Without re-doing the search, a clearer summary of the main criteria used to move an article from screening to full text review would be helpful.

Response: Thank you for your feedback on that. The results presented on this manuscript are part of a broader study that aimed at evaluating the cost and the preparedness/response strategies for infectious diseases in general. Hence, the search strategy refers to the complete dataset of identified studies. However, in our inclusion criteria we mention including only studies on respiratory infectious diseases within our final inclusion criteria due to the outbreak of COVID-19. In order to avoid any confusion, we added a brief explanation in the 'Methods' section.

Comment 3: Page 4, line 59 – the agreement % (837%) needs to be corrected

Response: Corrected

Comment 4: In the description of the process used to analyze the synthesis of cost-effectiveness, a statement of the usual comparator would be helpful (e.g., “no intervention”) would be helpful because the description of more, equally, or less effective or costly begs the question of “compared to what?” It’s mentioned later but would be helpful to describe earlier.

Response: Thank you for bringing this issue to our attention. We have added the comparators as per your suggestion.

Comment 5: When describing the quality of the studies included (top of page 6), what were the reasons the one study was only of medium quality?

Response: This study was rated at 58% and it was of medium quality due to some missing quality criteria not mentioned by authors including comparative intervention, sensitivity analysis, incremental costs & outcomes and whether there are conflicts of interest or not. This is now clearly presented in the Appendix

Comment 6: For Appendices 2-4, labels are needed on the X axis

Response: Thank you for your indication. We have added them.

Comment 7: Figure 2 – explanation of the color coding is needed in the footnote

Response: Thank you for your comment. The colors are linked to the symbols (-, +, 0) which are explained right below the table.

Comment 8: On page 8, Madema is referred to with the incorrect reference number (33). And is this a simulation model among developing countries? (in the table description it says ‘developed’)

Response: Thank you for noting that clerical error.

Comment 9: I think in general the reference numbers need to be double checked and updated.

Response: Thank you for noting that. We have carefully checked the references.

Comment 10: In the discussion of the stockpile strategy, was the cumulative costs over time taken into account? It seems like an important factor since the cost of maintaining it accumulates over years in which it is not needed, or at least talk about the average amount of time that the stockpiles remain unused.

Response: Indeed although interesting this information was not available. We noted this now in the discussion section of the manuscript.

Comment 11: I think some important limitations need to be mentioned given that this will inevitably be discussed in light of COVID-19. Specifically, the typical duration of the outbreak or the simulation, and/or the availability of pharmaceutical interventions such as vaccination, would have a substantial impact on both compliance with non-pharmaceutical interventions and on the economic impact of closures, with the acknowledgement that the long-term effects of potential school drop-out or business closures could not be assessed.

Response: Thank you for your important comment. We have included additional limitations in this section, such as publication bias due to the exclusion of non-English published

studies, additionally studies published before the pre-planned timeframe and the exclusion of seasonal influenza outbreaks.